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This report summarizes research during the past year on: the damage mechanism for short (80 ns) pulses of CO_2 laser radiation interacting with the cornea epithelium; epithelial damage from multiple-pulse exposures to more penetrating mid-infrared radiation from a Tm:YAG laser at 2.02 μm; and predictions of retinal damage thresholds for exposures to sources with rectangular irradiance distributions. Damage threshold measurements on corneas maintained at 21 C using single 80 ns pulses continue to support a thermal damage mechanism. For sequences of 25 ms pulses of 2.02 μm radiation at 10 and 20 Hz, the threshold energy density per pulse, ED_{th}, is related to the number of pulses by an equation of the form $ED_{th} = CN^{-\alpha}$ for $25 \le N \le 999$, but the relationship breaks down for $N<25$. These thresholds are not described by a critical temperature damage model for $N>50$ at 10 Hz and $N>200$ at 20 Hz. Retinal damage thresholds for rectangular beams were in excellent agreement with those for Gaussian beams having equal 1/e areas for shorter exposures (3 μs to 1 ms). For longer exposures (10 s), the agreement was good for beams with low aspect ratios, but it was only fair for beams with high aspect ratios.

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Russell L. McCally 12/11/98

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Introduction

The military employs a broad range of laser radiation in training devices, rangefinders, target designators, communications devices and other instruments. This equipment emits either single pulses or sequences of pulses in beams of various diameters. The research performed under this contract directly supports the U. S. Army Medical Research and Materiel Command (USAMRMC) mission to assess the health effects and hazards of non-ionizing electromagnetic radiation from such laser systems. The data obtained will support evaluation of current permissible exposure limits and will aid health policy makers, both within and outside the DoD, in developing injury prevention criteria. The general approach is to make direct determinations of damage threshold levels for non-ionizing radiation for specific exposure conditions (e.g., wavelengths, pulse durations, etc.) and to develop models of the damage mechanism that enable the extension of the results to other exposure conditions.

Under past support from the Army Medical Research and Development Command we determined corneal damage thresholds for CO_2 lasers that emit single and sequences of pulses having durations of 1 ms and longer and developed thermal damage models for predicting this type of damage.[1-5] We also determined corneal damage thresholds for single 80 ns pulses of CO_2 laser radiation and for three multiple-pulse exposures (2 pulses at 1 Hz; and 2 and 8 pulses at 10 Hz).[6, 7] In the case of these very short pulses, damage mechanisms other than thermal (e.g., acoustic pressure pulses) could also play a role. Light and electron microscopy revealed unusual disruptions of the anterior epithelial surface for corneas exposed to a single pulse near the damage threshold. The characteristics of these disruptions differed from those observed with simple thermal damage at longer pulse durations and appeared to be consistent with a mechanical (e.g., acoustic) damage mechanism. However, the calculated temperature increase produced by the threshold exposure was only slightly lower than that calculated for threshold exposures having durations of 1 ms and longer.[6, 7] Thus we could not exclude a thermal damage mechanism, with the sharp temperature gradients leading to marked differences in the character of the damage as compared to damage from longer duration exposures.

During the first two years of this study we expanded the database of thresholds for sequences of 80 ns CO_2 laser pulses to include larger numbers of pulses and other pulse repetition frequencies and performed experiments aimed at clarifying the damage mechanism(s). We found that threshold damage is correlated by a power law of the form $ED_{th} = CN^{-\alpha}$ in which ED_{th} is the threshold energy density and N is the number of pulses in the sequence.[8, 9] Temperature calculations revealed that the maximum temperature increase on the beam axis 10 μm beneath the anterior tear surface resulting from the different threshold exposures is essentially constant.[8] This result is consistent with a critical peak temperature damage model and suggests that, at least for the multiple-pulse exposures, the damage mechanism may be predominately thermal. Damage threshold measurements <u>for multiple-pulse exposures</u> on corneas maintained at 21 C suggested that the damage mechanism is indeed predominately thermal because the additional energy needed to produce damage was slightly greater than that required to raise the cornea temperature to its *in vivo* value.[8]

During the past contract year, the Simulation Training and Instrumentation Command (STRICOM) and the US Army Center for Health Promotion and Preventative Medicine (CHPPM) identified a soldier health and safety research issue with regard to the fielding of the MILES 2000 systems. They stated that additional biological effects modeling was required to assess the functional dependence ocular injury thresholds for exposures from sources which produce rectangular

irradiance distributions such as the laser diodes used in the MILES 2000 systems. A contract modification was made on Jan. 30, 1998 to address this issue.

This year we continued investigating the damage mechanism for short pulses of CO_2 radiation and began to address corneal damage in the mid-infrared spectral region where the radiation is more penetrating. We also began to assess the functional dependence of retinal injury thresholds for rectangular irradiance distributions in accordance with the contract modification made this year.

Methods

Short-pulse exposures are made with a Boston Laser (Model 220S) CO_2-TEA laser operated in the TEM_{00} mode. This laser delivers 80 ns pulses at pulse repetition frequencies up to 16 Hz. Mode quality is verified and the beam diameter is measured at the beginning, middle and end of each experimental session using a Spiricon linear pyroelectric array. The detector has 64 elements on 200 μm centers. It is mounted on a vertical micropositioner and is read out with a LeCroy 9354M digital oscilloscope. Pulse energy is measured with a Scientech detector immediately before and immediately after each exposure. A He-Ne alignment laser is incorporated in the setup to locate the position of the beam on the cornea.

Exposures in the mid-infrared spectral region are made with a Tm:YAG laser that was built by the Naval Research Laboratory (NRL) using APL funds. This laser produces radiation at 2.02 μm which was verified by measuring its output using a SPEX Minimate spectrometer with a 300 line/mm grating. Exposure duration and pulse rate are controlled with a Princeton Applied Research chopper. The chopper is used in conjunction with a Uniblitz shutter which acts as a gate to allow passage of the desired number of pulses.[5] Pulse duration and pulse repetition frequency are measured using the LeCroy 9354M digital oscilloscope. Beam diameter is controlled by means of a quartz lens and is measured at the point of interest by scanning with a knife edge.[10, 11] Beam irradiance is adjusted using a linear wedge neutral density filter that varies continuously from a an optical density of 0 to 1.0. A He-Ne alignment laser is incorporated in the setup to locate the position of the beam on the cornea.

New Zealand white rabbits of either sex weighing 4 - 5 pounds are used for the experiments. The rabbits are treated in accordance with the *Guide for the Care and Use of Laboratory Animals* (DHEW Publication No. (NIH) 85-23, Revised Edition, 1985) and with the Association for Research in Vision and Ophthalmology Resolution on the Use of Animals in Research. Prior to exposure the rabbits are anesthetized with an intramuscular injection of xylazine and ketamine hydrochloride (Rompun-Ketaset) in the proportions: 60% of 20 mg/ml Rompun to 40% of 100 mg/ml Ketaset by volume. In addition, a topical anesthesia (proparacaine hydrochloride 1/2%) is applied to each eye before exposure and a drop of homatropine bromide 5% is instilled to dilate the pupil. This facilitates examination of the exposed corneas for minimal lesions. The anesthetized animals are placed in a conventional holder for exposure. A speculum is inserted in the eye about one minute before exposure and the eye is irrigated with BSS solution (Alcon Surgical) which is at room temperature; however, in order to create a reproducible "tear film," the irrigation is stopped 20 sec before the exposure and excess fluid is blotted at the limbus. The cornea surface is assumed to have returned to its normal temperature after this time. One exposure is made to each eye. One-half hour after exposure the rabbits, still under anesthesia, are sacrificed with Beuthanasia-D administered in an ear vein. The eyes are enucleated and examined for damage using a Nikon FS-3 photo slit-lamp. In selected cases the globes are placed in gluteraldehyde/formaldehyde fixative and are delivered to Prof. W. R. Green's laboratory at the Wilmer Ophthalmological Institute for histology.

In a few experiments we exposed enucleated eyes which were at room temperature to test the damage mechanism for short pulses of CO_2 laser radiation. We have shown previously that reliable damage thresholds can be determined in freshly enucleated eyes.[12] For these experiments the rabbits were anesthetized and given a topical anesthesia and the pupils dilated exactly as was done for the *in vivo* exposures. The rabbits were then sacrificed and their eyes enucleated. The enucleated eyes were placed in room temperature (usually ~20 °C) BSS and allowed to equilibrate for at least 5 min. They were then exposed using the same protocol as for the *in vivo* exposures. After exposure the eyes were placed back in the BSS solution for 1/2 hr before examining them for damage.

The criterion that we use for minimal epithelial damage is that due to Brownell and Stuck,[13] namely the presence of a superficial gray-white spot that develops within 1/2 hr after exposure. We have found that the damage threshold is sharply defined; i.e., only rarely is there overlap between exposures that produce minimal lesions and those that do not. Therefore we do not use statistical procedures such as probit analysis in order to determine the threshold, as these would require the use of more animals than we deem necessary. We make one exposure per eye, bracketing exposures above and below threshold. The bracket is narrowed until there is only about a 10% difference in energy density or irradiance between an exposure that produces a minimal lesion and one that does not. The threshold exposure is taken to be at the center of the bracket.

Corneal temperature calculations are based on a Green's function solution to the heat conduction equation for a beam having a Gaussian irradiance profile incident on a semi-infinite slab. We assume that he beam is absorbed according to Beer's law and has a constant peak irradiance for the duration of each pulse. We also assume that conduction is the only mode of heat transfer and that no heat is lost to the air at the epithelial interface. The absorption coefficient and thermal properties are assumed to be those of water.[1, 2] The solution $T(r,z,t)$, where r is the radial distance from the beam axis, z is the depth into the cornea, and t is time, has the form of a definite integral that can be evaluated numerically.[1, 4, 14] The FORTRAN program for calculating the temperature history was included in a previous report.[8]

Retinal thermal calculations are made using an adaptation of the model introduced by Birngruber et al.[15] This model treats the retinal pigment epithelium (RPE) and choroid as thin homogeneous sheets of infinite extent that absorb radiation according to Beer's law. The surrounding media are assumed to be non-absorbing. The RPE, choroid, and surrounding media are all assumed to have the thermal properties of water. Convective heat transfer is ignored which is justified for relatively short exposures (less than a few seconds). Temperature histories are then governed by the heat diffusion equation. Solutions are obtained by integrating the fundamental Green's function with the source term.[16-18] Because we are primarily interested in the effects of beam geometry, we ignore the choroidal contribution.[18] As in the case of the cornea calculations, the solution $T(x,y,z,t)$, where x and y are orthagonal distances from the beam axis, z is the distance along the beam axis measured from the anterior portion of the RPE, and t is time, has the form of a definite integral that can be evaluated numerically.[18]

Results and Discussion

In the original Statement of Work we proposed to : (1) extend the data base to include more damage thresholds for sequences of CO_2-TEA laser pulses and to elucidate further the mechanisms responsible for this type of damage; (2) determine damage thresholds for continuous wave radiation at wavelengths between 1.3 and 2.6 μm using source(s) identified during the first year and begin to investigate multiple-pulse damage at these wavelengths; and, (3) extend theoretical damage models. In addition, the contract was modified this year to include a study of the functional

dependence of ocular injury thresholds for exposures to sources such as laser diodes which have rectangular irradiance distributions.

The first of the goals in the original Statement of Work had been essentially completed at the time annual report for the period 11/96 – 10/97 was issued and the results were reported there.[8] This year we did one remaining experiment to investigate the damage mechanism for the 80 ns pulses emitted by the CO_2-TEA laser, verified the operating characteristics of a Tm:YAG laser which operates at a wavelength of 2.02 μm, began to determine multiple-pulse damage thresholds using the Tm:YAG laser, and made temperature calculations in the retina for exposures from rectangular sources having various aspect ratios and exposure durations.

i. CO_2-TEA laser damage mechanism.

Histology from corneas exposed to a <u>single</u> 80 ns pulse showed features consistent with both thermal and mechanical damage,[6, 7] thus it is important to determine the relative importance of these two damage mechanisms. Last year we reported data suggesting that damage from <u>multiple-pulse</u> exposures to CO_2-TEA laser radiation is predominately thermal.[8] This conclusion was based on damage thresholds measured for corneas in enucleated eyes that were maintained at room temperature (21°C). We found that additional energy was required to produce minimal damage, and that the amount of additional energy was sufficient to raise the anterior cornea temperature to a level slightly higher than that which produces damage to corneas exposed *in vivo*. If the damage mechanism were predominately mechanical, we would have expected that the thresholds to be similar to those measured *in vivo*.

Table 1: Threshold Energy Densities and Calculated Maximum Temperature Rises for Corneas at Initially at Room Temperature (21 C) Compared to Corneas *in Vivo*.

Number of Pulses	Pulse Rep. Freq. (Hz)	ED_{th} (mJ/cm²/pulse) Room Temp. (21°C)	ED_{th} (mJ/cm²/pulse) *in vivo*	ΔT_{max} (C) Room Temp. (21°C)	ΔT_{max} (C) *in vivo*
1		537	307	52.9	30.25
8	16	393	205	59.8	31.26
32	16	236	150	51.6	32.9

Because the original histology showing features consistent with both damage mechanisms was done only for single-pulse exposures, we proceeded to determine the single pulse damage threshold for corneas in enucleated eyes at room temperature. The result is given in Table 1 together with the multiple-pulse results reported previously. The Table also lists the corresponding *in vivo* thresholds for comparison. The new data and calculations for the single-pulse exposure also are consistent with damage that is predominately thermal. If the *in vivo* temperature of the anterior cornea is assumed to be 35°C (308 K),[19] then the calculated "damage temperatures" are 338 K, 339 K and 341 K for the single-pulse and the 8- and 32- pulse exposures respectively, whereas they are 347 K, 353 K and 345 K at the corresponding conditions for corneas in enucleated eyes.

In all cases the additional energy required to produce a minimal lesion in the enucleated eyes is sufficient to raise the anterior cornea temperature to a level slightly higher than that which produces damage *in vivo.*

ii. Tm:YAG laser characterization

The Tm:YAG laser was built at the Naval Research Laboratory (NRL) using APL funds. The laser was completed in 1994 prior to the beginning of this contract, but it had not been used, except for initial verification of its operation, until this year. When we first tested the laser it had no output even though the laser diode pump lasers appeared to be operating properly. We had virtually no documentation describing details of the laser; however, we finally were able to contact Dr. Robert Stoneman who had built it (Dr. Stoneman is longer at NRL). He thought that the most likely problem was in the coupling of the pump laser output to the Tm:YAG crystal. The outputs of the three diode pump lasers are combined and delivered to the Tm:YAG crystal via a fiber optic. The output from the fiber optic is focused into the crystal and the position of the focused beam is adjustable with an x-y-z micropositioner. He said to use caution in moving the micropositioner because the diode output is sufficient to vaporize the indium foil heat sink that surrounds the crystal. We therefore proceeded with caution and quickly optimized the laser output at 350 mW.

When the laser was first received its output was ~600 mW. It is possible that the output side of the crystal is contaminated, but it is not accessible without totally disassembling the laser (we were strongly advised against taking this step). After consulting with our contracting officer's representative, Mr. Bruce Stuck, we decided to first use the laser at its present output level. We did several calculations of temperature histories for multiple-pulse exposures which suggested that we would be able to produce threshold damage for reasonable parameters.

We verified the operating wavelength of the laser by measuring its output with a monochromator. It was 2.02 µm as expected. We verified that the laser was operating in the fundamental TEM_{00} mode by directly viewing of the beam on a fluorescent screen and by profiling with a knife edge. The irradiance profile for a laser operating in the TEM_{00} is a Gaussian given by

$$I = I_0 \exp\left[\left(-r / r_{1/e}\right)^2\right], \tag{1}$$

where the irradiance on the beam axis, I_0, is equal to the total power in the beam divided by the area of the beam at the 1/e radius, $r_{1/e}$. The power measured as a knife edge is scanned in the x direction across such a beam is given by[10, 11]

$$P(x) = \frac{P}{2}\left\{1 - erf\left[\frac{(x - x_0)}{r_{1/e}}\right]\right\}, \tag{2}$$

where x_0 is the position of the center of the beam, P is the total power and *erf* is the error function. We use the program Mathematica to obtain a non-linear least squares fit to Equation 2 in terms of the three parameters $r_{1/e}$, x_0, and P_0. The results of a typical beam scan are shown in Figure 1. The fit indicates that the beam quality is excellent.

iii. Multiple-pulse damage thresholds.

We have measured epithelial damage thresholds for sequences of 25, 50, 200 and 999 pulses at frequencies of 10 and 20 Hz. The duration of the individual pulses was 25 ms and the nominal 1/e diameter of the beam was 1 mm. Figure 2 shows a typical lesion which resulted from an exposure

to 50 pulses at 20 Hz at an irradiance approximately 30% greater than the damage threshold. Lesions even slightly above threshold also are circular and well defined. The damage thresholds determined for both pulse repetition frequencies are compiled in Table 2.

The threshold energy densities (per pulse) from Table 2 are plotted as a function of the number of pulses in Figure 3. It is clear that the quantities are related by a power law of the form $ED_{th} = CN^{-\alpha}$. The straight lines are least squares fits to this equation, from which we found that the values of the parameters C and α are respectively 1.74 and 0.22 for the thresholds at 10

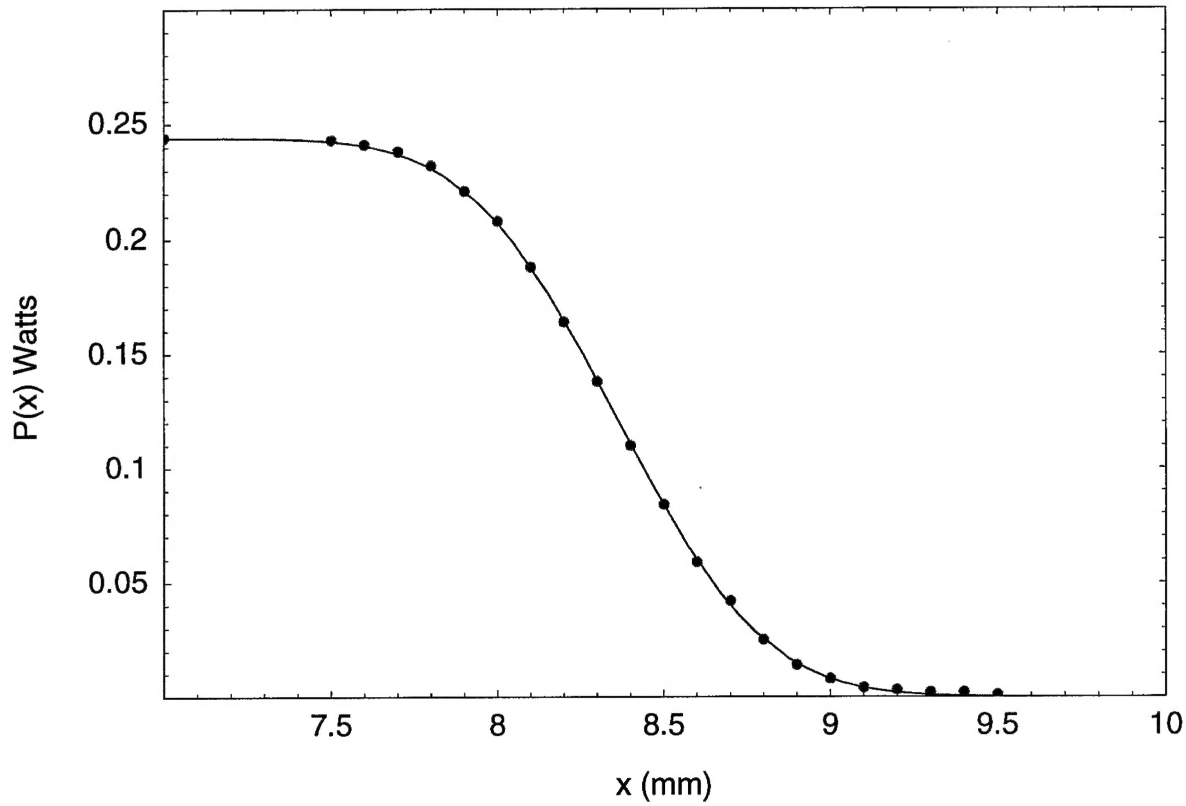

Figure 1: Profile of the Tm:YAG laser beam using a scanning knife edge. The solid line is a best least-squares fit to Equation 2, for which $r_{1/e}$ = 0.492 mm, x_0 = 8.359 mm, and P_0 = 0.244 W. For this fit, $\chi^2 = 1.7 \times 10^{-6}$, which indicates that the fit is excellent.

Hz and 1.31 and 0.22 for the thresholds at 20 Hz. For values of $N \geq 25$, the fits are parallel and therefore do not converge to a single value at $N = 1$. Moreover both fits predict a single-pulse threshold that is much lower than would be expected on the basis of previous data for single-pulse exposures.[12] These earlier data suggest that the single-pulse threshold would be approximately 2.5 J/cm^2 for a 25 ms exposure with a 1/e beam diameter of 1 mm. Unfortunately the maximum power output of the Tm:YAG laser (~0.3 W, which includes the reflective losses at the quartz focusing lens and the attenuator) precludes obtaining thresholds with 25 ms pulses and a 1/e beam diameter of ~1 mm for less than 25 pulses at 10 Hz and for less than about 10 pulses at 20 Hz. Therefore at present, we are not able to determine where the data begin to deviate from the power law dependence as the number of pulses is reduced.

Table 2: Tm:YAG Multiple-Pulse Damage Thresholds

N	*PRF* (Hz)	$r_{1/e}$ (mm)	I_{th} (W/cm^2)	ED_{th} (J/cm^2 /pulse)
25	10	0.468	35.0	0.875
50	10	0.492	29.2	0.730
200	10	0.505	19.6	0.490
999	10	0.509	15.5	0.388
25	20	0.508	25.4	0.635
50	20	0.492	22.2	0.556
200	20	0.486	17.4	0.435
999	20	0.492	11.2	0.280

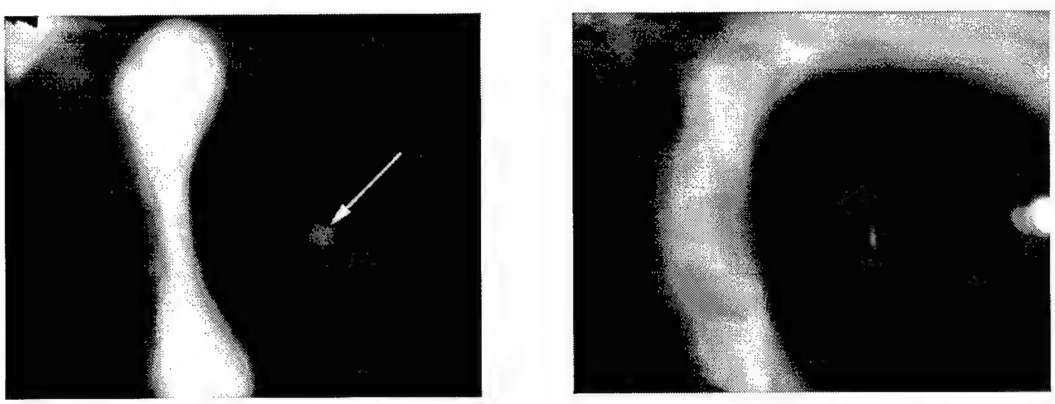

Figure 2: Broad- (left) and narrow-slit (right) views of a lesion (arrow in broad slit view) resulting from an exposure to 50 pulses from the Tm:YAG laser. The pulse repetition frequency was 20 Hz, the individual pulse duration was 25 ms, and the irradiance was 29.4 W/cm^2, which is approximately 30% above the damage threshold for these conditions.

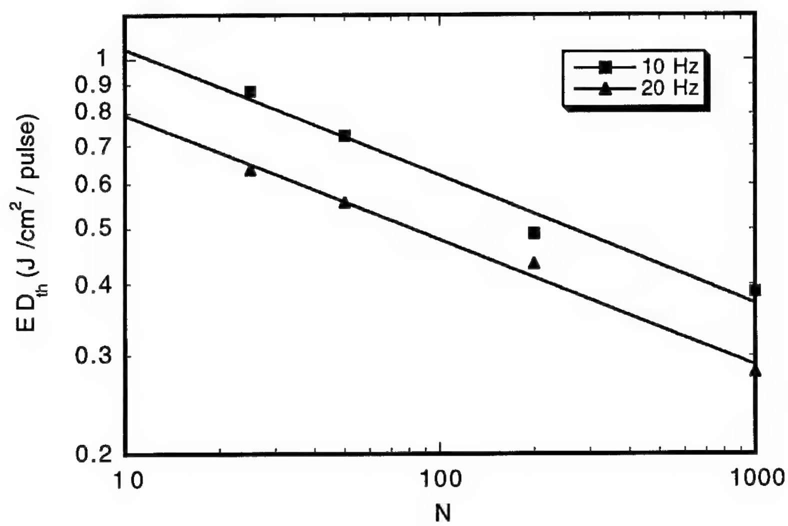

Figure 3. Dependence of the threshold energy density per pulse on the number of pulses. A least squares fit shows that the data are described by a power law of the form $ED_{th} = CN^{-\alpha}$. The R value is 0.99 for both fits.

A re-examination of epithelial damage threshold data for multiple-pulse CO_2 laser exposures (for 1ms pulses at 20 and 100 Hz)[5] which are reproduced in Figure 4 reveals similar behavior. If one concentrates only on the points for $N \geq 10$, these data also are approximately parallel. Moreover, as in the case of the Tm:YAG exposures, the data for the higher pulse repetition frequency lies below the data at the lower frequency and the data for $N \geq 10$ extrapolates to a single-pulse threshold that is much lower than the measured value.

These results for CO_2 and Tm:YAG damage show that, at least for these examples, there are substantial deviations from a strict power law dependence between the threshold energy density per pulse) and the number of pulses for small numbers of pulses.

We made calculations of temperature histories for the damage conditions listed in Table 2. The maximum temperature increases for the various exposures calculated at a point on the beam axis, 10 μm below the anterior tear surface are listed in Table 3. As noted previously, this location is just inside the anterior-most epithelial cells.[1, 5, 12] Previous studies found that epithelial damage thresholds for exposures to single-pulses of Tm:YAG and CO_2 radiation were correlated by a critical temperature damage model.[5, 12] In the case of Tm:YAG exposures the average critical temperature increase (also calculated at a point on the beam axis, 10 μm below the anterior tear surface) was 44° C for exposure durations between 0.082 and 4.28 sec.[12] In the case of the

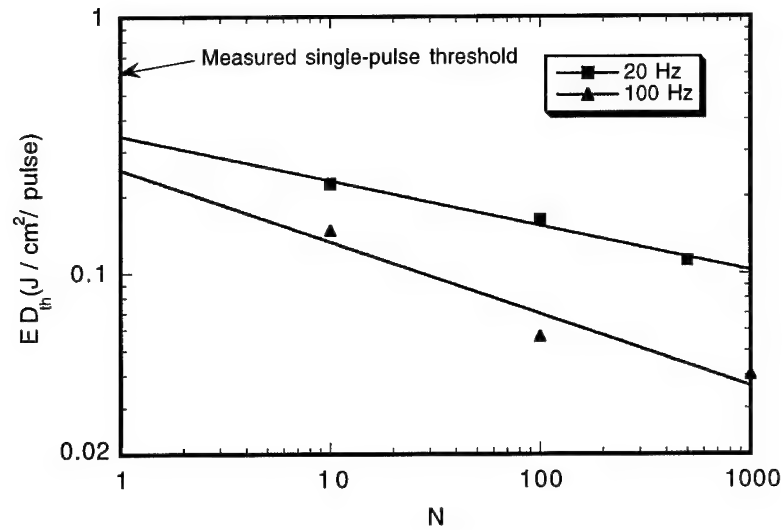

Figure 4. CO_2 laser epithelial damage thresholds taken from Bargeron et al.[5] The threshold energy density per pulse is shown as a function of the number of pulses at pulse repetition frequencies of 20 and 100 Hz. The individual pulse duration for the exposures was ~1 ms. The lines are fits to a power law of the form $ED_{th} = CN^{-\alpha}$ for $N \geq 10$.

CO_2 exposures, the critical temperature increase varied slightly for exposures between 1 ms and 10 sec and was described by a modified critical temperature law given by

$$\Delta T_{crit} = 37\tau^{-0.037} ; \qquad (3)$$

where τ is the exposure duration; however for exposures between 0.01 and 1 second, the increase was nearly constant with an average value of 40°C. Previous studies of multiple-pulse damage thresholds for CO_2 laser radiation found that damage was also reasonably well correlated by a critical temperature law, where the critical temperature again depended somewhat on the duration of the individual pulses.[5] For sequences of up to 999 pulses at repetition frequencies from 1 to 100 Hz, the critical temperature increases were 36.5 ± 3.6 °C, 43 ± 4.7 °C and 45.3 ± 3 °C for individual pulse durations near 1 ms, 10 ms and 300 ms respectively (± denotes the full range of values).[5] For a pulse duration of 80 ns, the maximum temperature increases were 30.8 ± 5 °C for sequences up to 999 pulses at frequencies of 10 and 16 Hz (where ± again denotes the full range of values).[8] In contrast, for sequences having greater than 50 pulses at 10 Hz and greater than 200 pulses at 20 Hz the multiple-pulse Tm:YAG exposures are not correlated by a critical temperature model. The reason for this breakdown is not yet understood.

Table 3: Maximum Temperature Increases for Tm:YAG Damage Thresholds*

N	*PRF* (Hz)	I_{th} (W/cm^2)	ΔT_{max} (°C)
25	10	35.0	34.6
50	10	29.2	32.3
200	10	19.6	24.7
999	10	15.5	20.9
25	20	25.4	38.9
50*	20	22.2	40.5
200*	20	17.4	38.8
999	20	11.2	27.8

* Calculated on the beam axis 10 μm below the anterior tear surface

iv. Retinal temperature calculations for rectangular irradiance distributions.

Retinal temperature calculations were made using methods described by Freund et al[18] and were done in close consultation with our colleagues Dr. David Sliney and Mr. Wes Marshall at CHPPM. In this initial study, the temperatures were calculated at a point on the beam axis, 4 μm in front of the pigment epithelium where the photoreceptors are located. We used an absorption coefficient for the retinal pigment epithelium that is appropriate for Argon laser radiation at 514 nm.[15] The damage threshold was determined by finding the irradiance for which the damage integral was equal to one for each exposure duration. Parameters in the damage integral were taken from Birngruber.[15] Calculations were done for rectangular beams whose width, $2a$, and height ,$2b$, varied among the values 25, 50, 100, 200, 500, 1000, 2000 μm; all possible combinations were considered. The exposure durations considered were 3μs, 10μs, 1ms, and 10s. For each such calculation, a similar calculation was done for a Gaussian beam having the same 1/e area (i.e., $r_{1/e} = 2\sqrt{(ab/\pi})$). The threshold irradiances obtained from these calculations were then used to compute the total energy predicted to cause damage and the thresholds for the rectangular and Gaussian beams were compared. For exposure durations of 3μs, 10μs, and 1ms, the total energies at the damage threshold for rectangular and Gaussian beams having equal 1/e areas were in excellent agreement. For the 10s exposure, the agreement was good for rectangular beams with low aspect ratios; but it was only fair for beams with high aspect ratios.

Conclusions

Measurements of epithelial damage thresholds for corneas exposed to a single 80 ns pulse from a CO_2-TEA laser show that more energy is required to produce damage in corneas maintained at 21 C than for corneas exposed *in vivo*. The amount of additional energy is slightly greater than that which would be required to raise the anterior cornea to its *in vivo* temperature which indicates that the damage mechanism is predominately thermal. This result is consistent with our findings reported last year for multiple-pulse exposures.

Corneal epithelial damage thresholds for multiple-pulse exposures to mid-infrared radiation from a Tm:YAG laser (wavelength 2.02 μm and individual pulse duration equal to 25 ms) are correlated by a power law of the form $ED_{th} = CN^{-\alpha}$,which relates the threshold energy density, ED_{th}, to the number of pulses in the sequence. For the cases we have investigated to date (pulse repetition frequencies of 10 and 20 Hz and $N \geq 25$), the constant C differs slightly depending on the pulse repetition frequency, but the exponent α is the same for both conditions. Because the exponent is the same, the power law (with different values of the constant C) predicts different values for the single-pulse threshold that are too low; therefore the relationship breaks down for small numbers of pulses. A re-examination of multiple-pulse thresholds for CO_2 radiation with an individual pulse duration of 1 ms, which also were correlated by a power law, showed that there was a similar breakdown in the relationship for small numbers of pulses.

Previous studies found that epithelial damage thresholds for exposures to single-pulses of Tm:YAG radiation and to both single- and multiple-pulses of CO_2 radiation were also correlated by a critical temperature damage model. In contrast, temperature calculations based on the thresholds for multiple-pulse exposures to Tm:YAG radiation show that the critical temperature damage model does not describe the data for large numbers of pulses.

Retinal damage thresholds were predicted for rectangular irradiance distributions such as those that would be produced by diode lasers. For shorter exposures (3 μs to 1 ms), the damage thresholds for rectangular beams were in excellent agreement with those for Gaussian beams having equal 1/e areas. For longer exposures (10 s), the agreement was good for rectangular beams with low aspect ratios; but it was only fair for beams with high aspect ratios.

References

1. C. B. Bargeron, R. L. McCally, and R. A. Farrell, "Calculated and Measured Endothelial Temperature Histories of Excised Rabbit Corneas Exposed to Infrared Radiation," *Exp Eye Res.* **32**, 241-250 (1981).

2. C. B. Bargeron, R. A. Farrell, W. R. Green, and R. L. McCally, "Corneal Damage from Exposure to IR radiation: Rabbit Endothelial Damage Thresholds," *Health Phys.* **40**, 855-862 (1981).

3. R. L. McCally, C. B. Bargeron, W. R. Green, and R. A. Farrell, "Stromal Damage in Rabbit Corneas Exposed to CO_2 Laser Radiation," *Exp. Eye Res.* **37**, 543-550 (1983).

4. R. A. Farrell, R. L. McCally, C. B. Bargeron, and W. R. Green, "Structural Alterations in the Cornea from Exposure to Infrared Radiation," *JHU/APL TG 1364* (1985).

5. C. B. Bargeron, O. J. Deters, R. A. Farrell, and R. L. McCally, "Epithelial Damage in Rabbit Corneas Exposed to CO_2 Laser Radiation," *Health Phys.* **56**, 85-95 (1989)

6. R. A. Farrell, R. L. McCally, C. B. Bargeron, and W. R. Green, *Structural Alterations in the Cornea from Exposure to Infrared Radiation*, U.S. Army Medical Research and Development Command, Fort Detrick, MD 21701-5012 (1989).

7. R. A. Farrell, C. B. Bargeron, R. L. McCally, and W. R. Green, "Corneal Effects Produced by IR Laser Radiation," in *Laser Safety, Eyesafe Laser Systems, and Laser Eye Protection*, Los Angeles, California, 59-70 (1990).

8. R. L. McCally, *Corneal Damage from Infrared Radiation*, Annual Report to the AMRMC, Contract DAMD17-96-C-6005 (1997).

9. R. L. McCally and C. B. Bargeron, "Epithelial Damage Thresholds for Sequences of 80 ns Pulses of 10.6 μm Laser Radiation," *Jour. of Laser Appl.* **10**, 137-139 (1998).

10. J. M. Khosrofian and B. A. Garetz, "Measurement of a Gaussian Laser Beam Diameter by the Direct Inversion of Knife-edge Data," *Appl. Optics* **22**, 3406-3410 (1983).

11. R. L. McCally, "Measurement of Gaussian Beam Parameters," *Appl. Optics* **23**, 2227 (1984).

12. R. L. McCally, R. A. Farrell, and C. B. Bargeron, "Cornea Epithelial Damage Thresholds in Rabbits Exposed to Tm:YAG Laser Radiation at 2.02 μm," *Lasers in Surgery and Medicine* **12**, 598-603 (1992).

13. A. S. Brownell and B. E. Stuck, "Ocular and skin hazards from CO_2 laser radiation," *Proceedings of the 9th Army Science Conference* **1**, 123-138 (1974).

14. H. C. Chang and K. G. Dedrick, "Corneal Damage Thresholds of CO_2 Laser Radiation," *Appl. Optics* **8**, 126-127 (1969).

15. R. Birngruber, F. Hillenkamp, and V. P Gabel, "Theoretical Investigations of Laser Thermal Retinal Injury," *Health Physics* **48**, 781-796 (1985).

16. P. M. Morse and H. Feshbach, *Methods of Theoretical Physics,* McGraw-Hill, New York (1953).

17. H. S. Carslaw and J. C. Jaeger, *Conduction of Heat in Solids*, Clarendon Press, Oxford (1959), pp. 1-49.

18. D. E. Freund, R. L. McCally, R. A. Farrell, and D. H. Sliney, "A Theoretical Comparison of Retinal Temperature Changes Resulting from Exposure to Rectangular and Gaussian Beams," *Lasers in the Life Sci.* **7**, 71-89 (1996).

19. R. F. Rosenbluth and I. Fatt, "Temperature Measurements in the Eye," *Exp. Eye Res.* **25**, 325-341 (1977).